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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/538,171 | 12/08/2005 | Hagit Eldar-Finkelman | 29724 | 4524 |

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| EXAMINER | |
|---|---|
| RUSSEL, JEFFREY E | |
| ART UNIT | PAPER NUMBER |
| 1654 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/538,171 | ELDAR-FINKELMAN, HAGIT | |
| | Examiner | Art Unit | |
| | Jeffrey E. Russel | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8,10-12,14-17,24-26,28,46-49,63-65,67,71-74,88,89,97-99,101,163 and 167* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050914*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,6-8,10-12,14-17,24-26,28,46-49,63-65,67,71-74,88-90,93-99,101,118-125,127-129,131-135,141-146,148-150,152-156,162,163 and 167.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 90,93-96,118-125,127-129,131-135,141-146,148-150,152-156 and 162.

1. Applicant's election of the species treatment of non-insulin dependent diabetes mellitus, in the reply filed on July 5, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 90, 93-96, 118-125, 127-129, 131-135, 141-146, 148-150, 152-156, and 162 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 5, 2007.

2. The Sequence Listing filed June 9, 2005 is approved.

3. The disclosure is objected to because of the following informalities: At pages 7, 14, 15, and 23 of the specification, the meaning of the circled words "Deleted: X" is not known. It is not clear if these words are to be inserted into the specification, or if these words indicate that "X" has been deleted from the paragraph. The amendment format is not compliant with 37 CFR 1.121(b). Appropriate correction is required.

4. Instant claims 1, 2, 4, 6-8, 10-12, 14-17, 24-26, 28, 46-49, 63-65, 67, 71-74, 88, 89, 97-99, 101, 163, and 167 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional applications 60/432,644 or 60/482,719, because the provisional applications, under the test of 35 U.S.C. 112, first paragraph, do not disclose, e.g., conjugates of the general formula recited in independent claim 1, where n can range from 16 to 50 and where the hydrophobic moiety can be attached to any part of the polypeptide. Accordingly, the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980) is available as prior art against the instant claims under 35 U.S.C. 102(a).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

6. Claims 1, 2, 4, 6-8, 10-12, 14, 15, 46-49, 63-65, 71-74, 88, and 89 are rejected under 35 U.S.C. 102(a) as being anticipated by the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980). The Plotkin et al article teaches a GSK-3 inhibitor designated L803-mts and having the structure recited in Applicant's claims, i.e. comprising a N-terminal myristoyl group, an alanine residue at the positions corresponding to Applicant's Z and $Y_3$ residues, n=6, and m=1. See page 975, column 2, second full paragraph. L803-mts has the same amino acid sequence as Applicant's SEQ ID NO:16. L803-mts also corresponds to the structure recited in Applicant's claims in which n=1 and the N-terminal sequence GKEAP comprises a hydrophobic

peptide sequence AP. The inhibitor is dissolved in 0.1% DMSO buffer solution (see page 975, column 1, second full paragraph), which corresponds to Applicant's pharmaceutically acceptable carrier. The inhibitor inhibits the ability of GSK-3 to phosphorylate a peptide substrate; is administered in vitro to HEK 293 cells and to mouse adipocytes, optionally followed by contacting the mouse adipocytes with suboptimal amounts of insulin; and is administered to insulin-resistant obese mice and improves their glucose tolerance. See, e.g., the Abstract; page 975, column 2, second full paragraph, through page 976, column 1, second full paragraph; and Figure 1.

7. Claims 16, 17, and 163 are rejected under 35 U.S.C. 103(a) as being obvious over the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980). Application of the Plotkin et al article is the same as in the above rejection of claims 1, 2, 4, 6-8, 10-12, 14, 15, 46-49, 63-65, 71-74, 88, and 89. The Plotkin et al article does not teach packaging the L803-mts with instructions for use. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to package the L803-mts with instructions for use because it is routine to package pharmaceutical compositions with instructions for use because it eases storage, transportation, measurement, and administration of the pharmaceutical composition. The Plotkin et al article does not teach forming L803-mts by reacting myristic acid with the peptide portion of the inhibitor. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the L803-mts of the Plotkin et al article by reacting myristic acid with the peptide portion of the inhibitor, because peptide conjugates are routinely formed in the art by reacting the peptide portion of the conjugate with the modifying

agent, and because the method of synthesis would not have been expected to affect the activity of the resulting peptide conjugate.

8. Claims 24-26, 28, 63-65, 67, 97-99, and 101 are rejected under 35 U.S.C. 103(a) as being obvious over the Plotkin et al article (J. Pharmacol. Exp. Therapeutics, Vol. 305, pages 974-980) as applied against claims 1, 2, 4, 6-8, 10-12, 14, 15, 46-49, 63-65, 71-73, 88, and 89 above, and further in view of the American Diabetes Association article (Diabetes Care, Vol. 17, pages 616-623) or the WO Patent Application 01/49709. The Plotkin et al article does not teach co-administration of GSK-3 inhibitors such as insulin and ingredients capable of downregulating an expression of GSK-3 when administering L803-mts in vivo. The American Diabetes Association article teaches insulin administration as a standard practice when treating patients with NIDDM. See page 617, column 3, first full paragraph. The WO Patent Application '709 teaches co-administering ingredients capable of downregulating an expression of GSK-3 when treating patients with NIDDM. See, e.g., page 19, line 17 - page 20, line 10. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to combine treatment with L803 as taught by the Plotkin et al article and treatment with insulin as taught by the American Diabetes Association article or treatment with ingredients capable of downregulating an expression of GSK-3 as taught by the WO Patent Application '709, because co-administration of active agents when treating NIDDM is known as taught by the American Diabetes Association article and by the WO Patent Application '709, and because co-administration of active agents would have been expected to increase the probability of effective treatment.

9. Claims 1, 2, 4, 11, 12, 15, 24-26, 28, 46-49, 63-65, 67, 71-74, 88, 89, 97-99, 101, and 163 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 01/49709. The WO Patent Application '709 teaches a GSK-1 inhibitor, designated peptide #8 (see page 30, Table 1), which corresponds to Applicant's conjugate in which n=1, a hydrophobic moiety comprising the hydrophobic peptide sequence Ala-Pro is attached to the N-terminus of the polypeptide, m=1, and the residue corresponding to Applicants' Z residue is alanine. The WO Patent Application '709's inhibitors are combined with pharmaceutically acceptable excipients and carriers. See, e.g., page 18, lines 3-7, and page 20, lines 11-30. The inhibitors inhibit GSK-3 in vitro in cell-based assays. See, e.g., Example 3 and claim 8. The inhibitors are used to potentiate insulin signaling and to treat non-insulin dependent diabetes mellitus. See, e.g., page 9, line 20 - page 10, line 9, and page 25, lines 7-29. The inhibitors can be co-administered with, e.g., lithium, which is a GSK-3 inhibitor, or an antisense or ribozyme molecule which downregulates expression of GSK-3. The inhibitors can be co-administered with insulin until insulin potentiation obviates the need for administration of exogenous insulin. See, e.g., page 19, line 17 - page 20, line 10, and Example 4. The WO Patent Application '709's peptide inhibitors can be synthesized by Merrifield synthesis (see page 15, lines 18-28), which will result in hydrophobic amino acids/moieties being attached to a peptide portion of the inhibitor corresponding to Applicant's polypeptide.

10. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 01/49709. Application of the WO Patent Application '709 is the same as in the above rejection of claims 1, 2, 4, 11, 12, 15, 24-26, 28, 46-49, 63-65, 67, 71-74, 88, 89, 97-99, 101, and 163. The WO Patent Application '709 does not teach packaging its inhibitors with

instructions for use. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to package the inhibitors of the WO Patent Application '709 with instructions for use because it is routine to package pharmaceutical compositions with instructions for use because it eases storage, transportation, measurement, and administration of the pharmaceutical composition.

11. Claims 1, 2, 4, 6-8, 10-12, and 167 are rejected under 35 U.S.C. 102(b) as being anticipated by the Taniguchi et al article (J. Biol. Chem., Vol. 269, pages 18299-18302). The Taniguchi et al article teaches the protein MARCKS, which is myristoylated at the N-terminus; which comprises polypeptides, e.g., the sequence AQFSKTAAKGEATAERPGEAAVASS*P (see residues 2-27 of MARCKS), corresponding to Applicant's amino acid sequence in which n=20, $Y_3$ is G, Z is Ala, and m=1. See Figure 3. The Taniguchi et al article also teaches peptide fragments, e.g., K8 which comprises a hydrophobic peptide sequence PAAAA attached to the N-terminus of a polypeptide corresponding to Applicant's amino acid sequence in which n=1, Z is Asp, and m=1 or 2, e.g., the sequence PDAGAS*PV. Note that the additional amino acids which are present as part of the Taniguchi et al article's MARCKS and peptide fragments are not excluded from Applicants' claimed conjugates in view of the "comprising" language at claim 1, line 1. Other analogous correspondences between MARCKS and its fragments and Applicant's claimed conjugates are clearly present. In view of the similarity in structure between the MARCKS and its fragments of the Taniguchi et al article and Applicant's claimed conjugates, inherently the MARCKS and its fragments of the Taniguchi et al article will be capable of inhibiting an activity of GSK-3, and inherently the myristoyl group and/or hydrophobic peptide sequences present in the MARCKS and its fragments of the Taniguchi et al article will provide

the conjugate with better membrane permeability and/or interaction with the hydrophobic patch of GSK-3, to the same extent claimed by Applicant. Sufficient evidence of similarity is deemed to be present between the MARCKS and its fragments of the Taniguchi et al article and Applicant's claimed conjugates to shift the burden to Applicant to provide evidence that the claimed conjugates are unobviously different than the MARCKS and its fragments of the Taniguchi et al article.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

August 9, 2007